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NIOSH is evaluating breast cancer incidence in two large, previously assembled cohorts of workers. One of the cohorts includes approximately 10,000 women with exposure to ethylene oxide (ETO), a direct alkylating agent which produces mammary tumors in mice. The other cohort includes over 13,000 women exposed to polychlorinated biphenyls (PCBs), a group of chemicals suspected to be carcinogenic to the breast because of their lipophilic and estrogenic activities. Each cohort represents the largest and best defined female study cohort in the U.S. for the respective exposure. The primary activities for this year have focused on: a) identifying mailing addresses for individuals in the two study cohorts, b) identification of next-of-kin for deceased individuals, c) acquisition of medical records for cancer deaths, and d) obtaining approval to provide an Assurance of Confidentiality for the study as allowed by section 308(d) of the Public Health Service Act. Address identification is virtually complete for living members of the cohort and the first phase of data collection will start in October of 1997.

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Elizabeth Ward 9/30/97

PI - Signature Date

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INTRODUCTION

Nature of the Problem

Breast cancer is the most common incident cancer among U.S. women, and the second leading cause of cancer mortality in U.S. women.[1] Increasing numbers of women are employed outside the home. Few studies of breast cancer etiology have addressed occupational and environmental chemical exposures, and many cancer studies of industrial cohorts have excluded women.[2] Occupational exposure to carcinogens may be of particular concern when the exposures occur during periods of rapid cell division, such as during pregnancy or lactation.[2]

Only recently has the importance of studying occupational cancer among women workers been recognized.[3] Identification of carcinogenic hazards among women workers is of benefit not only to individuals with occupational exposures, but also to the general population, if identification of a hazardous chemical leads to reduction of environmental exposure.

NIOSH is evaluating breast cancer incidence in two large study cohorts, which have been previously assembled. One of the cohorts includes 9,929 women with exposure to ethylene oxide (ETO), a direct alkylating agent which produces mammary tumors in mice.[4,5] The other cohort includes over 13,000 women exposed to polychlorinated biphenyls (PCBs), a group of chemicals suspected to be carcinogenic to the breast because of their lipophilic and estrogenic activities. Each cohort represents the largest and best defined female study cohort in the U.S. for the respective exposure.

Background

The incidence of breast cancer in the U.S. has increased in the past two decades.[1] Known epidemiologic risk factors for breast cancer include a family history of breast cancer, early age at menarche, nulliparity or late age at first birth, and later age at menopause.[6] It has been hypothesized that exposure to chemicals in environmentally contaminated food is related to the increasing incidence of breast cancer.[7] According to this hypothesis, chemicals that bioaccumulate in fatty tissues and those that are estrogenic are most likely to be associated with breast cancer risk. Many chlorinated hydrocarbons, including 2,3,7,8-tetrachlorodibenzo-p-dioxins, PCBs and some pesticides are lipophilic and estrogenic to varying degrees. One recent study found elevated PCB concentration in the mammary tissue of patients with breast cancer compared to patients with benign breast disease.[8] Another study did not find a significant association between serum PCB concentration and risk of breast cancer, but did find a significant association for DDE (a metabolite of DDT).[9] According to the International Agency for Research on Cancer (IARC) rating scheme, PCBs are probable human carcinogens[10] with sufficient evidence from experimental animal studies to classify PCBs as carcinogenic, but limited evidence from human studies.

Agents that act directly on DNA, such as radiation and chemical alkylating agents, have also been

shown to be carcinogenic in mammary tissue in animal studies and in humans.[7] Although the chemicals that induce breast cancer in humans are not well-defined, it is reasonable to suspect that chemicals that produce mammary tumors in rodent bioassays may also be breast carcinogens in humans.[11] IARC has determined that ETO is a carcinogen based on limited evidence in humans and sufficient evidence in animals (IARC, 1987).[10] The IARC determination was based primarily on leukemia and brain cancer in animals, and leukemia in humans. However, there was also some evidence of mammary cancer in animals and breast cancer in humans exposed to ETO.

Thus, the proposed study has two subsets: 1) a cohort of women exposed to PCBs, a class of compounds suspected to be breast carcinogens because of their lipophilic and estrogenic activities, and 2) a cohort of women exposed to ETO, a direct alkylating agent which produces mammary tumors in animals.

Study Objectives

The study has the following primary objectives:

a. To evaluate whether exposure to ETO or PCBs is associated with increased breast cancer.

b. To identify incident cases of breast cancer in the ETO and PCB cohorts and to collect information on exposures and relevant risk factors by questionnaire surveys of living women and the next-of-kin of deceased women.

c. To determine whether the incidence of breast cancer is elevated in each cohort (ETO and PCB) compared to the general population, controlling for non-occupational factors that may be associated with both breast cancer risk and employment status (i.e., nulliparity, age at first birth).

d. To evaluate the exposure-response relationship within each cohort (ETO and PCB), controlling for non-occupational risk factors.

e. If either study (ETO or PCB) is positive, to provide data for risk assessments to estimate risk in the general population.

BODY

Methods

Given the high survival rates for women diagnosed with breast cancer (>75% for white women and >60% for black women), cancer incidence is a much more sensitive indicator of increased risk than cancer mortality. Longstanding population-based cancer registries are available for only one of the three PCB facilities, which is located in New York State (Massachusetts and Indiana have newer registries that will also be used) and three of the 14 ETO plants. Thus, cancer incidence for both cohorts will have to be primarily determined through the use of questionnaires. Registry matching will be done for the plants in areas covered by population based-registries since this will provide an additional means of identifying cases, particularly for individuals who could not be contacted. The questionnaire approach also allows the collection of data on non-occupational risk factors, which are required for the full interpretation of the incidence study results.

Exposure Assessment

Ethylene oxide. NIOSH has assembled by far the largest existing cohort of ethylene oxide-exposed workers (n=18,000). This cohort includes 9,929 women, contributing 196,788 person-years of observation through 1991. All were exposed in the commercial sterilization industry. The average year of first exposure was 1970, and the average length of exposure was 5 years. Considerable effort was spent in developing an estimate of ETO exposure for each worker in the study for each of their jobs held throughout employment. Over 2,300 personal samples were obtained for the 1979-1985 period at 13 different plants, and these as well as knowledge of historical processes were used to estimate exposures. The resulting "job-exposure" matrix has been cited as one of the better estimates of historical exposures in occupational epidemiology, and it permits quantitative dose-response analyses which can rarely be done in most historical epidemiologic studies. Average ETO exposures in this cohort were 2-3 ppm in the 1970s and 1980s, with higher exposures occurring in the 1960s. Using the job-exposure matrix, we will be able to determine whether the risk of breast cancer increases with increasing dose.

Polychlorinated biphenyls. The particular PCB compound used at each capacitor plant varied over time. The three plants ceased using PCBs in 1976 or 1977. Serum PCB measurements are available for only a small fraction of workers. Although it is not feasible to construct an exposure matrix for PCBs based on air concentrations (because of the limited number of air samples available and potential for dermal absorption of PCBs), we will be able to classify jobs as having had high, medium or low exposure. Thus we can determine whether the risk of breast cancer rises with increased dose.

Classification of jobs by high, medium, or low exposure will be done primarily by the department and job in which an individual worked. Duration and calendar period of exposure will also be taken into account. The type of exposure data that is available

varies by company; all industrial hygiene and other relevant data (e.g., serum data) which have been collected at all three companies will be considered. For the first company, descriptions of jobs and tasks, and identification of the highest exposed group are available from a prior NIOSH study. For the second company, the above information is available plus the company has serum data that NIOSH has requested. In addition, a plant survey and interviews of long-term workers and foremen were conducted in 1993. For the third company, descriptions of jobs and tasks are available from a prior NIOSH study, and NIOSH collected serum PCB data from a sample of workers. In addition, plant survey information, worker interviews, and records of raw materials and production processes are available from this facility. Factors to be considered in classifying exposure include the opportunity for direct exposure to PCBs (e.g., dermal exposure), air sampling measurements for specific job titles, and degree of chlorination of the PCB mixture used at a particular time.

Data Analysis

Two types of analyses of breast cancer incidence will be conducted. The first analysis will evaluate the risk of occupational exposure within each cohort, controlling for non-occupational risk factors by stratification or modeling. This analysis will be restricted to those for whom data on confounding variables are available, and thus will be restricted to respondents (either living or next-of-kin), or nonrespondents from whom data on confounding variables can be obtained from another source (e.g., medical records). This internal analysis will compare those with higher exposure to those with lower exposure. In the analysis of the ethylene oxide cohort, the dose matrix based on historical ethylene oxide air concentrations will be used to conduct a quantitative dose-response analysis. For the PCB cohort, duration of exposure in high, medium, and low exposure jobs will be analyzed, as well as ever/never employment in such jobs. For both analyses, the exposure-response relationship will be evaluated using regression analyses (e.g., Cox and Poisson regression). The direct control over confounders and the potential to analyze dose-response relationships give this first analysis advantages over the second analysis described below.

The second analysis will answer the question of whether the incidence of breast cancer in the study cohort is higher than that expected in the general population. This analysis, which does not require data on confounders for each subject (see below) will include those women for whom it is possible to ascertain that they did or did not have breast cancer, based on all possible sources. Analyses will compare the observed population to the U.S. population for the combined exposed group and by categories of cumulative exposure. The number of incident breast cancers expected in the cohort if they were developing breast cancer at the same rate as the general population will be calculated using the NIOSH life table analysis system (LTAS). A referent rate file will be constructed using data from the SEER (Surveillance, Epidemiology, and End Results) population. This population combines data from a number of state and city registries and represents about

14% of the U.S. population. It is frequently used as a referent population in epidemiologic studies and is commonly taken to be reasonably representative of the entire U.S. population. Rates from the relevant state cancer registries may also be considered for comparison where appropriate. The potential effect of non-occupational risk factors that may act as confounders because they are related to both employment status and disease, such as age at first birth, parity, and socioeconomic status, will be estimated using methods developed to assess the effects of smoking habits on lung cancer risk in occupational cohorts.[12] This method relies on determining the differences between exposed and nonexposed populations with respect to known confounders, and adjusting the observed breast cancer rate ratio between exposed and nonexposed to account for such differences, using the known relationships between such confounders and breast cancer rates. Data on the distribution of confounders in the exposed population will be available from the questionnaire. Data on the distribution of confounders in the nonexposed U.S. referent population will be obtained from published survey data, such as the data on parity in the U.S. population available from fertility tables for different birth cohorts. Known relationships between confounders and breast cancer will be obtained from large published epidemiologic studies.

Progress to Date

The accomplishments this year have focused primarily on ascertainment of current mailing address for potential study participants, identification of next-of-kin for deceased workers, acquisition of medical records, and approval to provide an Assurance of Confidentiality to protect study data. The specific activities to date have included:

Task 1, Conduct Vital Status Follow-up:

a. Update vital status through 1995 using the National Death Index; obtain death certificates and code all underlying and contributory causes of death.

   This task is essentially complete for the original study cohorts. Several hundred additional workers from one study company that were not originally included have been identified through recent records obtained from the company and are now being traced. If eligible, these workers will be included in future questionnaire mailings.

b. Obtain current addresses and phone numbers of all living members of the study cohort or their next-of-kin through data supplied by the Internal Revenue Service, the U.S. Post Office, case-location services and telephone directories.

   This task is essentially complete for living members of the original study cohorts. Work has begun to identify next-of-kin for deceased workers through death

certificates, medical records, and pension forms obtained from selected study companies.

Task 2, Prepare for Data Collection Phase of Study:

a. Obtain clearance for the questionnaire study from the NIOSH Human Subjects Review Board (HSRB) and OMB approval.

OMB and HSRB approval has been obtained. Because of concerns that sensitive data collected in this study may be released under the routine uses of the Privacy Act, we obtained approval for an Assurance of Confidentiality which is allowable under section 308(d) of the Public Health Service Act. This approval, in addition to preventing unauthorized disclosure of study data, requires that strict security measures be in place both at NIOSH and at Battelle to protect the study data. The extra security precautions have the added potential benefit of increasing study participation, thereby improving the scientific validity of the study.

b. Prepare a Request for Negotiated Contract to collect breast cancer incidence data, and award contract competitively.

The Request for Negotiated Contract was written and the contract was awarded to Battelle/Survey Research Associates.

Task 3, Collect Questionnaire & Medical Record Data:

Questionnaires have been developed, pretested, finalized, and printed. The first mailing to living cohort members is scheduled for October of 1997. The questionnaires have been entered into a Computer-Assisted Telephone Interview (CATI) program to maximize data quality and ease of entry during telephone interviews with non-respondents to the mailings.

All study materials (questionnaires, cover letters, consent forms) have been translated into Spanish and Portuguese to accommodate individuals in the New Bedford, Massachusetts area who are known to be primarily of Cape Verdean descent. Spanish and Portuguese-speaking interviewers have been hired to conduct telephone interviews with non-respondents to the mailings.

Medical records are being obtained for all cancer deaths, as identified from death certificates. A total of 298 medical records of 609 requested (49%) have been obtained to date. Battelle is developing a tracking system for the acquisition of medical records for cancers reported on the questionnaire.

Task 4, Data Analysis & Completion of Final Report:

No activity during this time period.

CONCLUSIONS

The primary activities for the third year have focused on establishing mailing addresses for individuals in the two study cohorts, identifying next-of-kin for deceased cohort members, obtaining medical records for cancer deaths, and seeking approval for an Assurance of Confidentiality allowable under Section 308(d) of the Public Health Service Act. Work to accomplish these tasks has proceeded in a timely fashion. Questionnaire mailings are scheduled to begin in October of this year.

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